CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-323

Forest Laboratories, Inc.
Attention: Robert W. Ashworth, Ph.D.
Senior Director, Regulatory Affairs
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Ashworth:

Please refer to your new drug application (NDA) dated March 23, 2001, received March 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg Tablets.

We acknowledge receipt of your submission dated February 28, 2002. Your submission of February 28, 2002 constituted a complete response to our January 23, 2002 action letter.

This new drug application provides for the use of Lexapro for the treatment of major depressive disorder.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

We note your agreement to the attached labeling in an e-mail communication dated August 14, 2002.

Additionally, we note your agreement, conveyed in your February 28, 2002 resubmission, to adopt the following dissolution method and specification for all strengths of the Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg Tablets:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle Speed:	50 RPM
Medium:	900 mL 0.1N HCL at 37°C
Specification:	NLT — in 30 minutes

We also refer to your fax transmission on August 5, 2002, in which you provided additional ECG information for escitalopram. In particular, we reference your analysis of plasma concentration and change from baseline in QTc interval in study MD-01. We ask that you provide, postapproval, a more complete report on your analysis, including a listing of individual plasma concentrations and the corresponding values for change from baseline in

QTc interval.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-323." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
8/14/02 03:51:08 PM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-323

Forest Laboratories, Inc.
Attention: Daniel Coleman, Ph.D.
Manager, Regulatory Affairs
Plaza 3, Suite 602
Harborside Financial Center
Jersey City, NJ 07311

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated March 23, 2001, received March 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 20 mg Tablets.

We acknowledge receipt of your following submissions dated: March 28, April 10, May 18, May 24, July 12, August 13, September 4, September 27, October 9, October 16, October 19, October 22, December 6, December 19, 2001, and January 9, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Clinical

1. **Labeling**

   Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of Escitalopram in the treatment of major depressive disorder (MDD). We have used, as our base labeling, the labeling submitted in your October 19, 2001 amendment. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling.

   We are also taking this opportunity, in a class labeling initiative, to change the indication from the more broad terminology of depression to major depressive disorder. Our primary concern is whether product labeling accurately describes the condition for which approval was granted. Broad terminology, such as depression, cannot adequately communicate distinct, specific indications to the reader of product labeling. Therefore, we feel that the **INDICATIONS** section of labeling fails to furnish adequate information for the safe and effective use of the drug.

   To correct these longstanding deficiencies in the wording of the **INDICATIONS** section and in references to this section that occur in other parts of labeling, we are asking sponsors to revise labeling to more precisely reflect that these agents are indicated for the treatment of major depressive disorder. Implicit in this request

is our presumption that approval for depression was predicated on studies conducted predominantly in patients diagnosed with major depressive disorder.

2. Safety Update

Our assessment of the safety of escitalopram is based on our review of all safety information provided in your original and subsequent submissions, including your safety updates dated May 24, July 12, and October 19, 2001. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

3. Regulatory Status Update

Please provide any new information on the regulatory status of escitalopram worldwide, i.e., information available subsequent to the regulatory status update provided in your March 23, 2001 submission.

4. Worldwide Literature Update

Please provide an updated worldwide literature search for both citalopram and escitalopram.

5. Proposed Tradename

Please refer to our Agency letter dated September 26, 2001, informing you that your proposed tradename of —— was unacceptable. However, your proposed proprietary name of Lexapro was given tentative approval by the Agency. Your resubmission should address whether you intend to use Lexapro as the tradename so that the Agency can assess whether final tradename approval may be given.

6. Request for Additional Cardiac Data

We refer to a request for additional cardiac data for escitalopram made on November 30, 2001. We acknowledge that these data have now been received in submissions dated December 19, 2001, and January 9, 2002, and they are under review.

Preclinical Toxicology

We are concerned that the chronic toxicity studies performed in rats with racemic citalopram may not predict important toxicities that might be associated with chronic treatment with escitalopram.

Our acceptance of a 13 week rat toxicity bridging study as constituting an adequate assessment of the long-term toxicity of escitalopram presupposed that the findings seen with escitalopram would be essentially similar to those seen with the racemate at appropriate doses. If this were the case, the results of the chronic toxicology studies done with the racemate could reasonably be assumed to predict the findings with chronic escitalopram use.

However, in our view, this turned out not to be the case. Specifically, there was evidence of cardiac injury at the 80 mg/kg/day dose of escitalopram in both the 13 week and 60 day studies, but there was little evidence of these cardiac lesions in the racemate treated groups, including at the maximum dose of 160 mg/kg/day. These lesions did not seem to be related to higher levels of S-citalopram (or of the 2 main metabolites) in the escitalopram treated animals compared to the racemate treated animals, because the plasma levels (either Cmax or AUC) were not substantively different between the groups. Because this injury was not seen in the racemate treated animals, this raises questions about the validity of the long-term toxicity studies performed with the racemate as a predictor of the long-term toxicity of escitalopram. This may be particularly problematic in this case, because, for example, the margin of safety for S-citalopram (AUC at the NOEL of 40 mg/kg/day in the 13 week rat study, compared to the AUC of a 20 mg dose in humans) is only about 2; it is possible that this ratio may decrease with longer duration of treatment in the rat. Such a lesion, were it to occur in humans, could not easily be detected at an early stage.

For these reasons, you will need to justify our continued reliance on the chronic citalopram toxicology data as being adequate to predict the chronic toxicity of escitalopram.

Clinical Pharmacology and Biopharmaceutics

We ask that you agree to the following recommendation by our Office of Clinical Pharmacology and Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:	USP Apparatus 2 (Paddle)
Paddle Speed:	50 RPM
Medium:	900 mL 0.1N HCL at 37°C
Specification:	NLT — in 30 minutes

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL